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Canadian Adverse Drug Reaction Newsletter

Therapeutic Products Programme

IN THIS ISSUE:

•ACE inhibitors and bronchospasm
•Interferon beta-1b
•Radiopharmaceuticals
•New Expert Advisory Committee on Pharmacovigilance

New name

The Drugs Programme and the Medical Devices Programme were merged late in 1996. As of May 1, 1997, we became the Therapeutic Products Programme. We are still the same people, doing the same jobs, at the same locations, and we look forward to continuing to work with you!

ACE inhibitors and bronchospasm

Angiotensin-converting-enzyme (ACE) inhibitors approved in Canada are indicated for the treatment of mild to moderate essential hypertension. Some ACE inhibitors are also indicated for congestive heart failure or diabetic nephropathy or for use after myocardial infarction. Those available in Canada are benazepril hydrochloride, captopril, cilazapril, enalapril maleate, enalaprilat, fosinopril sodium, lisinopril, perindopril erbumine, quinapril hydrochloride and ramipril.

A dry, tickly, persistent and often bothersome cough is one of the most common adverse effects of ACE inhibitors that has emerged as a class effect and seems to be independent of the dose. This symptom may occur shortly after therapy is started but also months or even a year later. The cough will usually resolve within a few days after withdrawal of the ACE inhibitor.<1> The relationship between ACE inhibitors and bronchial hyperresponsiveness, however, has not been as clearly established.<2> It has been proposed that ACE inhibitor-induced bronchospasm may be caused by potent bronchoconstrictors such as bradykinin and substance P, which are degraded by ACE and may accumulate in the lungs of patients receiving ACE inhibitors.<2> It has also been postulated that an ACE inhibitor-induced cough may be due to an irritant inflammatory state in the airways of susceptible patients and that this symptom may have pathophysiological features in common with the cough seen as an early symptom of asthma.<3> However, other mechanisms of ACE inhibitor-induced cough and bronchospasm have been proposed, and the exact mechanism involved still remains unknown.<1,4>

Although ACE inhibitors are safe for use in most patients with obstructive airway disease, there have been occasional reports of asthmatic symptoms, exacerbation of asthma or a rise in bronchial reactivity; however, these findings have not been universal.<1,2> Two large retrospective studies have evaluated reported adverse respiratory reactions associated with ACE inhibitors. One, a controlled cohort study in New Zealand, found a significantly higher occurrence of new-onset bronchospasm and a relapse of previous bronchospasm in the cohort treated with an ACE inhibitor than in the control group given lipid-lowering drugs.<1,2,5> In the other study,<6> based on data from the Swedish Drug Information System, a number of patients were identified in whom ACE inhibitors apparently had caused or worsened asthmatic symptoms or dyspnea. Some patients developed respiratory symptoms with different ACE inhibitors, which suggested a class effect rather than an allergic reaction to a specific substance.

A review of the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) database, over 15 years, revealed 126 reports involving ACE inhibitor-associated respiratory disorders. Of these, 82 included coughing reactions and 11 included various combinations of reactions reported as dyspnea, bronchospasm or asthma with or without cough. (Cases of bronchospasm reported as being part of a wider allergic process, such as anaphylaxis or angioedema, were excluded from this review.) The 11 reports of interest involved 10 patients (7 women and 3 men, age range 43-73 years) and are summarized in Table 1. Five patients were receiving an ACE inhibitor for hypertension and 1 for congestive heart failure; no indication was specified for the remaining 4 patients.

There were 7 instances (in 6 patients) in which symptoms resolved after the therapy was stopped. One patient (cases 9 and 10) experienced the same symptoms after being exposed to 2 different ACE inhibitors at different times. In both instances the symptoms disappeared after the therapy was stopped. In another patient the ACE inhibitor was stopped and Ventolin® was given as treatment, but the patient's outcome was not specified. Two patients who experienced shortness of breath died; however, both had confounding disease states, which precludes any definitive association with the ACE inhibitors. Finally, one patient received significant treatment for acute shortness of breath and asthma, but further to a rechallenge the physician reported that the adverse event was not related to the ACE inhibitor. It is unclear how this assessment was made.

The onset of symptoms ranged from a few hours to 6 months after the start of the ACE inhibitor therapy; 3 cases occurred within a few hours, 5 within less than 1 month and 2 after 3 to 6 months; the time of onset was not specified in 1 case.

Controversy still exists regarding the role of ACE inhibitors in inducing bronchospasm and the precipitation of asthmatic symptoms. These reactions appear to be rare, but health care professionals should be aware that they can occur.<7> Any suspected bronchospasm or aggravated asthma should be carefully monitored. Discontinuation of the ACE inhibitor is usually required.<6>

This article is under the direction of: Ann Sztuke-Fournier, BPharm

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Table 1: Details of 11 reports of dyspnea, bronchospasm and asthma associated with the use of angiotensin-converting-enzyme (ACE) inhibitors

Case	Age/sex	Reaction	Suspect drug	Other drugs/relevant history	Outcome
1	43/F	Exacerbation of asthma, including increased mucous production and bouts of coughing	Capoten	Ventolin aerosol, Atrovent aerosol, Beclovent aerosol, Quibron-T/SR Asthma	Coughing stopped 2 d after Capoten stopped; asthma medication unchanged
2	70/M	Increase in shortness of breath, cough, following increase in dosage of Capoten	Capoten	Previously: Apresoline, chlorthalidone, Slow-K; all stopped when Capoten initiated Hypertension, obesity and arthritis	Patient died 15 d after start of Capoten
3	64/F	Progressive development of dyspnea and bronchospasm	Capoten	Uniphyl, Berotec aerosol, Hygroton, Minipress	Capoten stopped after 9 mo; patient recovered
4	71/F	Dry, hacking cough and wheezing on exertion 2 wk after start of Capoten; late-onset asthma diagnosed 2 mo later; condition worsened 1½ yr later	Capoten	Alupent, Hismanal and other antihistamines, Beconase Aq.	Capoten stopped after 2 yr. Cough stopped but slight wheezing continued for 2 wk, then stopped
5	38/F	Minimal bronchospasm 3 wk after start of enalapril therapy; resolved. Dermatitis on hands later. Significant episode of bronchospasm and continuing cough 2 mo after start of ACE inhibitor	Vasotec	Ventolin	Vasotec stopped after 2 mo
6	71/F	Dyspnea, hacking cough within 2 d after start of captopril	Captopril	EC ASA, digoxin Congestive heart failure	Captopril stopped after 14 d; patient recovered
7	44/F	Acute shortness of breath, asthma attack after about 3 mo of Monopril therapy; seemed to have allergic conjunctivitis	Monopril	Prednisone (60 mg in decreasing doses over 3 wk), Ventolin aerosol, Becloforte aerosol	Monopril stopped; rechallenge after 3 mo. Physician reported that ADR not related to Monopril
8	73/F	Shortness of breath; no cough or fever	Enalapril	Folic acid, Coumadin, Cipro	Patient died. Autopsy findings: respiratory failure probable cause of death; septic shock due to pulmonary emboli or cardiogenic or occult bleed
9	63/M	Shortness of breath and wheezing 3 h after each dose of enalapril	Enalapril		Enalapril stopped after 1 mo; patient recovered
10*	63/M	Shortness of breath, breathlessness, wheezing and dyspnea	Prinivil		Patient given Prinivil 5 mo after enalapril stopped; same reaction as with enalapril. Prinivil stopped after 2 wk; patient recovered
11	55/M	Acute exacerbation of asthma	Zestril	Ventolin, Beclodisk Asthma, hypertension	Zestril stopped after 3 d; patient recovered

*Same patient as case 9.

Help wanted!

Because ADR reports are a critical source of drug safety information, the CADRMP is seeking your help in detecting and reporting ADRs. Reports on the use of drugs in different patient populations, concomitant drug use, duration of therapy and patient compliance are helpful. Your continued support is crucial in building a more complete drug safety profile. The CADRMP is grateful to all who are so diligently reporting suspected ADRs.

Interferon beta-1b

Betaseron®, an interferon beta-1b approved in July 1995, is indicated for use in ambulatory patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. Because Canada is one of the first countries to approve interferon beta-1b, data on ADRs associated with its use are limited.

Radiopharmaceuticals

Although approved radiopharmaceuticals, kits and generators have been used for diagnosis and therapy in Canadian nuclear medicine facilities for years, the rate of reporting ADRs resulting from these products is low.

The CADRMP strongly encourages voluntary reporting by health care professionals of ADRs associated with the administration of all marketed drugs. ADRs should be reported to the Adverse Drug Reaction Reporting Unit, Continuing Assessment Division, Bureau of Drug Surveillance, AL 4103B1, Ottawa ON K1A 1B9, fax 613 957-0335; or to a participating regional centre (check the *CPS* Clin-Info section on ADR reporting for complete addresses).

New Expert Advisory Committee on Pharmacovigilance

The Therapeutic Products Directorate (newly merged from the Drugs and Medical Devices Directorates) of Health Canada has established a new Expert Advisory Committee on Pharmacovigilance. This committee replaces the Canadian Adverse Drug Reaction Advisory Committee (CADRAC). It has a broader scope than that of CADRAC and will provide the directorate with on-going and timely advice on issues related to post-approval safety, quality and effectiveness of drug products. Decisions on regulatory issues will continue to be made by the Therapeutic Products Directorate.

The new advisory committee comprises 8 members selected on the basis of their knowledge and expertise in different disciplines related to post-approval drug surveillance: family and clinical medicine, pharmacy, pharmacology, pharmacoepidemiology, geriatrics, pediatrics, and poison information and control. It will identify specific issues and concerns, provide advice on matters of science and policy, assess adverse drug reaction (ADR) reports and drug product complaints, and evaluate drug safety issues related to misuse, abuse or off-label use. In the interest of enhancing professional and consumer awareness of post-approval drug surveillance issues, the committee will be invited to suggest topics for this newsletter and to recommend educational programs or other interventions, as deemed appropriate.

The terms of reference for the committee are posted on the Therapeutic Products Programme external electronic bulletin board and at **www.hwc.ca/hpb/drugs**, where minutes of future meetings will also be posted. For information on the Expert Advisory Committee on Pharmacovigilance, contact the coordinator: Malle Jurima-Romet, PhD, tel 613 957-9026, fax 613 941-8933.

Expert Advisory Committee on Pharmacovigilance

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Read us on the Internet!

You can now find the *Canadian Adverse Drug Reaction Newsletter* on the Therapeutic Products Programme external electronic bulletin board and at **www.hwc.ca/hpb/drugs/drhtmeng/publicat.html** Questions related to these services should be directed to Pete Nilson, tel 613 941-1601; fax 613 941-0825; **tp_webmaster@inet.hwc.ca**

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